REMARKS

Status of the Claims

Claims 1-11 and 13-17 are pending in the present application. Claims 5-10, 13 and 14 are withdrawn from consideration by the Examiner. Claim 12 is cancelled. Claim 2 has been amended so that the phrase "...an aspartic enzyme having homology to..." in paragraph (d) reads "...an aspartic enzyme having N-terminal amino acid sequence homology to..." The basis for this amendment may be found at page 9, lines 17-19 of the specification.

Rejection Of Claim 17 Under 35 U. S. C. 112, First Paragraph

Claim 17 is rejected by the Examiner under 35 U.S.C. 112, first paragraph, for the reasons set forth in paragraph 7 of the Office Action. The Examiner alleges that the following limitation in claim 17 includes new matter: "which is inhibited by an aspartic protease inhibitor." This rejection is respectfully traversed. Reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner should note that the above-mentioned limitation is supported at page 19, lines 14-24 of the specification and also by Figs. 5-6. Accordingly, no new matter has been incorporated into claim 17.

More specifically, the relevant description expressly teaches that "the activity of the enzyme of the present invention was

completely inhibited by pepstatin A, a specific inhibitor to an aspartic enzyme" as shown in Fig. 5.

In conclusion, the rejection of claim 17 under 35 U.S.C. 112, first paragraph, should be withdrawn by the Examiner in view of the remarks hereinabove.

Rejection Of Claims 2, 3 and 15 Under 35 U.S.C. 112, Second Paragraph

Claims 2, 3 and 15 are rejected by the Examiner under 35 U.S.C. 112, second paragraph, for the reasons set forth in paragraph 8 of the Office Action. This rejection is respectfully traversed. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim 2 has been amended to recite the phrase "N-terminal amino acid sequence homology" in place of the term "homology." Clearly, the claimed homology relates to N-terminal amino acid sequence homology. Accordingly, the rejection of claims 2, 3 and 15 under 35 U.S.C. 112, second paragraph, should be withdrawn by the Examiner.

Rejection of Claims 1-4, 11 and 15-17 Under 35 U.S.C. 102(e) as Being Anticipated by U.S. Patent No. 5,800,814

Claims 1-4, 11 and 15-17 are rejected by the Examiner under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,800,814 (hereinafter "the '814 patent") for the reasons set forth in paragraph 9 of the Office Action. This rejection is respectfully traversed. Reconsideration and withdrawal of this rejection are respectfully requested.

The Present Invention

The present invention as recited in claim 1 relates to an aspartic enzyme that produces plasma protein fragments having an inhibitory activity to metastasis and growth of cancer.

The present invention as recited in claim 2 relates to the enzyme of claim 1, which has the following properties:

(e) it has a molecular weight of about 45 kDa as measured by SDS electrophoresis under non-reduced condition;

(f) it has the N-terminal amino acid sequence LVRIPLHKFT (SEQ ID NO:1);

(g) it degrades plasma proteins at an acidic pH range of not more than pH 5.0 to produce plasma protein fragments having an inhibitory activity to metastasis and growth of cancer; and

(h) it is an aspartic enzyme having N-terminal amino acid sequence homology to a cathepsin D precursor.

The present invention as recited in claim 17 relates to an aspartic enzyme that produces plasma protein fragments having an inhibitory activity to metastasis and growth of cancer wherein said enzyme is active in an acidic pH range and which is inhibited by an aspartic protease inhibitor.

Distinctions Between the Present Invention and USP 5,800,814

Briefly, Applicants respectfully submit that the '814 patent fails to expressly or inherently disclose the claimed aspartic enzyme.

The present invention relates to an aspartic enzyme that produces plasma protein fragments having an inhibitory activity to metastasis and growth of cancer. See claim 1. The claimed aspartic enzyme has an N-terminal amino acid sequence homology to a cathepsin D precursor and degrading plasma proteins at an acidic pH range not more than pH 5.0. See claim 2. As a result, the claimed aspartic enzyme produces plasma protein fragments having the claimed inhibitory activity. Note claim 1.

The Examiner should further note that the desired inhibitory activity to metastasis and growth of cancer is not directly made by the claimed aspartic enzyme. Rather, the claimed inhibitory activity is obtained by the plasma protein fragments that are

produced by the enzymatic activity of the claimed enzyme from plasma proteins such as plasminogen. The resulting plasma protein fragments are an angiogenesis inhibitor that inhibits angiogenesis necessary for proliferation of cancer cells to thereby attain the inhibitory activity to metastasis and growth of cancer.

In contrast to the present invention, the '814 patent relates to a method for inhibiting the proliferation of breast cancer cells. This method comprises administering to the cells antibodies that bind with cathepsin D activation peptide and which inhibit binding of procathepsin D activation peptide to the breast cancer cells.

Further, the '814 patent discloses that:

(i) Cathepsin D is an aspartic protease with a pH optimum close to 3 (col. 1, line 12, col. 2, lines 46-47);

(ii) The activation of procathepsin D is accomplished by the removal of the 44 amino acid activation peptide at the N-terminus of the proenzyme (col. 2, lines 41-43, etc.);

(iii) Procathepsin D shows a mitogenic activity on breast cancer cells (col. 3, lines 24-26, col. 9, lines 35-57, Example 1, Fig. 1, etc.);

(iv) Mitogenic activity is exerted through the activation peptide but not through the proteolytic activity of cathepsin D (col. 3, lines 34-35, col. 4, lines 35-39, col. 5, lines 11-13, Examples 2-3, Figs. 2-3, etc.); and

(v) Mitogenic activity of procathepsin D may be blocked by antibodies to procathepsin D, in particular antibodies to the activation peptide, to thereby inhibit the proliferation of breast cancer cells (col. 3, lines 27-30, col. 6, lines 63-66, Examples 2-3, Figs. 2-3, etc.).

The N-terminal amino acid sequence, particularly amino acid residues 1-11, is common between the aspartic enzyme of the present invention and the activation peptide disclosed in the cited '814 patent. However, the Examiner should note that the activation peptide *per se* [with the 44 amino acid residues], is never an enzyme and does not have an enzymatic activity.

Contrary to the Examiner's assumption, it is cathepsin D and not the activation peptide that is an aspartic protease with a pH optimum close to 3.

As for procathepsin D, which includes the activation peptide at its N-terminal, this proenzyme is taught by the '814 patent to exhibit a mitogenic activity to breast cancer cells, i.e. an activity to enhance proliferation of breast cancer cells. The '814 patent further teaches and demonstrates that this mitogenic activity is due to the activation peptide present in procathepsin D but not due to the proteolytic activity of cathepsin D.

Accordingly, based on these teachings, the '814 patent ultimately discloses that blockage of the mitogenic activity by the activation peptide, e.g. by antibodies to the activation peptide or

to procathepsin D, would lead to inhibition of proliferation of breast cancer cells. This is in fact the invention of the cited '814 patent.

Contrary to the position taken by the Examiner, there is no teaching of an aspartic enzyme that produces plasma protein fragments having an inhibitory activity to metastasis and growth of cancer as in the present invention. In particular, the Examiner should note that the activity of procathepsin D containing the activation peptide with the N-terminal amino acid sequence identical to that of the claimed enzyme is a mitogenic activity to enhance proliferation of breast cancer cells. In contrast, the relevant activity of the claimed aspartic enzyme is an inhibitory activity to metastasis and growth of cancer, although the claimed activity is not directly achieved but is achieved by producing plasma protein fragments having the claimed inhibitory activity. In other words, the '814 patent discloses an entirely different activity of a proenzyme as compared to the claimed enzyme, namely a mitogenic activity to breast cancer cells attributable to the activation peptide in procathepsin D. This activity is in sharp contrast to an inhibitory activity to metastasis and growth of cancer attainable by the present invention.

Accordingly, the teachings of the cited '814 patent are entirely distinct from that of the present invention. Hence, the present invention not anticipated by the teachings of the '814

patent.

Law of Inherency

Briefly, since the Examiner provides no evidence that the activation peptide of the '814 patent has the claimed activity, Applicants respectfully submit that the rejection is not tenable. As such, Applicants respectfully request that the rejection be withdrawn.

To support a rejection based upon inherency, an Examiner must provide factual and technical grounds establishing that the inherent feature *necessarily* flows from the teachings of the prior art. See Ex parte Levy, 17 USPQ2d 1461 (BOPAI 1990); see also In re Oelrich, 212 USPQ 323 (CCPA 1981) holding that inherency *must* flow as a necessary conclusion from the prior art, not simply a possible one. The Examiner has failed to support his rejection consistent with applicable case law.

The Federal Circuit stated in In re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999), that "to establish inherency, extrinsic evidence must make clear that the missing descriptive matter was necessarily present in the thing described in the reference, and would be so recognized by persons with ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a set of circumstances is not sufficient." In re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999).

Further, it has been held that the mere fact that a certain thing may result from a given set of circumstances is not sufficient, and occasional results are not inherent. MEHL/Biophile International v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999).

Further, the Examiner has no basis for restating or repackaging this rejection under 35 U.S.C. 103. That which is inherent in the prior art, if not known at the time of the invention, cannot form a proper basis for rejecting the claimed invention as obvious under § 103. See In re Shetty, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 756-57 (C.C.P.A. 1977).

Arguments based on inherent properties cannot stand when there is no supporting teaching in the prior art. In re Spormann, 363 F.2d 444,448, 150 U.S.P.Q. 449 (C.C.P.A. 1966). Inherency and obviousness are distinct concepts. Thus, an applicant may in certain circumstances attack an obviousness rejection as improper if the Examiner indicates that specific features of the application, although not shown in the prior art, are inherent.

Since there is no evidence that the prior art teaches or suggests that the '814 patent discloses an aspartic enzyme that produces plasma protein fragments having an inhibitory activity to metastasis and growth of cancer, then Applicants respectfully submit that the rejection is not tenable. As such, Applicants respectfully request that the rejection be withdrawn because the

Examiner has no basis for alleging that the claimed invention is inherent in the prior art.

In conclusion, the rejection of claims 1-4, 11 and 15-17 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,800,814 for the reasons set forth in paragraph 9 of the Office Action should be withdrawn by the Examiner.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Marc S. Weiner (Reg. No. 32,181) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $120.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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